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Total syntheses of hyacinthacine A_2 and 7-deoxycasuarine by cycloaddition to a carbohydrate derived nitrone

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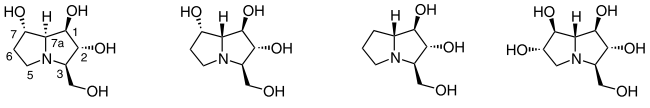
Abstract—Practical syntheses of nitrone **8** by two different approaches from sugars are reported. Its use as a versatile intermediate in highly selective 1,3-dipolar cycloaddition reactions constitutes the key step for novel total syntheses of hyacinthacine A_2 (**3**) and 7-deoxycasuarine (**20**) by simple transformations of a common isoxazolidine adduct.

Necine bases are known since long time as constituents of pyrrolizidine alkaloids.[1] On the contrary, 3-(hydroxymethyl)pyrrolizidines have been isolated from natural sources only recently, alexine (**1**)[2] and australine (**2**)[3] being the first examples of this family of alkaloids. Polyhydroxylated pyrrolizidine alkaloids with a hydroxymethyl substituent at C-3 rather than at C-1 have long been thought to be of very restricted natural occurrence.[4] More recently, a relevant number of heavily hydroxylated pyrrolizidines of this type have been isolated, like hyacinthacine A_2 (**3**),[5] casuarine (**4**),[6] and a number of their diastereoisomers and structural analogs,[7] which belong to these new classes of the alexines/australines and hyacinthacines.



alexine (**1**) australine (**2**) hyacinthacine A_2 (**3**) casuarine (**4**)

Many of these alkaloids possess potent glycosidases inhibition activity,[5,8] which makes them good candidates as new drugs for the treatment of many diseases such as viral infections, cancer and diabetes.[9] Consequently, these compounds became attractive synthetic targets and their high potential for therapeutic applications has prompted many efforts for devising general strategies for accessing them and their congeners.[10–12]

In this communication we report the synthesis of the trisubstituted chiral nitrone **8**, which has the correct relative and absolute stereochemistry at C-1, C-2 and C-3, as required for the above mentioned pyrrolizidine alkaloids. Its huge synthetic potential in this field is exemplified by the application to unprecedently straightforward and convenient syntheses of hyacinthacine A_2 (**3**) and 7-deoxycasuarine (**20**) by means of 1,3-dipolar cycloaddition reactions.[13]

Two different approaches for the synthesis of **8**[14,15] were pursued (Scheme 1), which gave quite comparable results in terms of overall yield. Both of them are based on intramolecular S_N2 reactions carried out by an oximate anion, which occur with inversion of configuration at the attacked carbon atom.[18] The first one,[19] which employs L-xylose as chiral building block, has its major drawback in the high cost of *O*-tetrahydropyranylhydroxylamine and of the starting sugar.[20] The second procedure, based on the synthesis of a related tribenzylated nitrone derived from D-ribose recently described by Holzapfel and co-workers,[18a] starts from D-arabinose and is to be preferred in terms of cost of the materials employed.

In order to study the behaviour of this new nitrone in 1,3-dipolar cycloadditions, **8** was reacted with maleic and acrylic acid derivatives **12**–**14** in CH_2Cl_2 at room temperature (Scheme 2). With dimethyl maleate (**12**), nitrone **8** reacted cleanly to afford exclusively the adduct **15**, whose relative stereochemistry as deriving from an *anti–exo* approach[13a] was firmly established on the basis of COSY and NOESY experiments. Albeit the formation of a unique adduct contrasts with the

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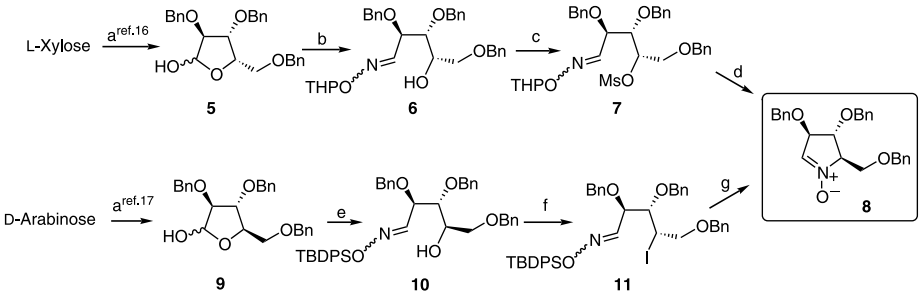
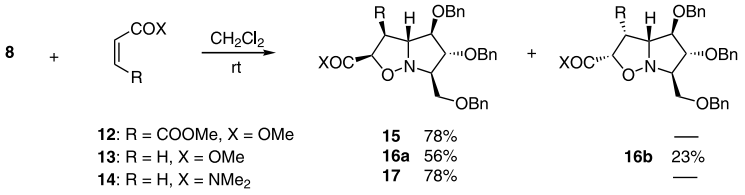


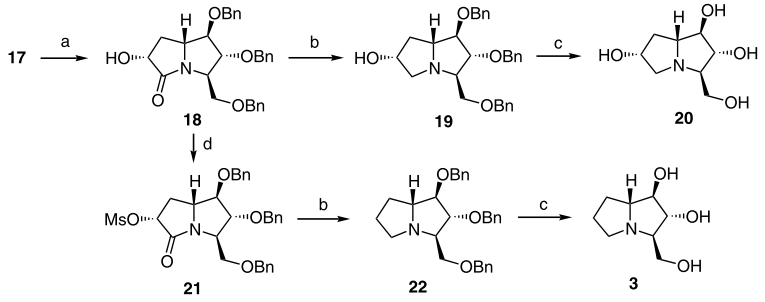
Scheme 1. *Reagents and conditions*: (a) i. MeOH/H_2SO_4, anhydr. Na_2SO_4, rt, 21 h; ii. BnCl/KOH, Na_2SO_4, reflux, 8 h; iii. 6N HCl, CH_3COOH, 60–70°C (50% over three steps); (b) NH_2OTHP, no solvent, rt, 6 d, 100%; (c) MsCl, TEA, CH_2Cl_2, rt, 24 h, 50–70%; (d) i. DOWEX 50W X8, MeOH, rt, 24 h, 96%; ii. 0.1 M NaOH, dioxane, 0°C, 2 h, 55%; (e) i. $NH_2OH{\cdot}HCl$, py, rt, 24 h; ii. TBDPSCl, py, rt, 18 h, 100%; (f) I_2, ImH, Ph_3P, toluene, reflux, 1 h, 48%; (g) TBAF on silica gel, benzene, reflux, 1.5 h, 91%.



Scheme 2.

stereoisomeric mixtures produced with malic and tartaric acids derived nitrones,[13a] it parallels the high selectivity displayed by a trisubstituted pyrroline nitrone possessing a similar stereochemical pattern.[21] In contrast, methyl acrylate (**13**) gave a mixture of the *anti* adducts **16** with a scarce 2.4:1 *exo* selectivity. Approaches of dipolarophiles **12** and **13** occurred exclusively *anti* to the benzyloxy group at C-3 and to the benzyloxymethyl group at C-5 of the nitrone, which are located on the same side of the ring. This stereoselectivity afforded relative stereochemistry as desired at C-1/C-7a in the final target molecules. The benzyloxy group at C-4, which was expected to hamper formation of *endo* cycloadducts,[13a,21] was indeed effective with maleate **12**, that led to exclusive formation of the *exo* adduct **15**, but not with methyl acrylate (**13**), which gave a relevant amount of the *endo* adduct **16b**. We reasoned that on increasing the steric demand of the dipolarophile, the *endo* mode of approach should be disfavoured. To our delight, use of the bulkier *N*,*N*-dimethylamide **14** allowed complete stereoselectivity of the cycloaddition to be restored in favour of the *anti–exo* adduct **17** (Scheme 2), possessing the stereochemistry required by casuarine at C-6.

The pyrroloisoxazolidine **17** was converted into the desired pyrrolizidines **20** and **3** by simple three- and four-step sequences, respectively (Scheme 3). Reductive cleavage of the N–O bond[13] with Zn in AcOH afforded the lactam **18** in good yield, which was transformed into 7-deoxycasuarine (**20**) through reduction with $LiAlH_4$ and removal of the benzyl protecting groups by hydrogenation over Pd. 7-Deoxycasuarine (**20**) was obtained with spectral data (^1H and ^{13}C NMR in D_2O) identical to those reported recently,[12d] but as a white solid [mp 205–208°C (dec.), $[\alpha]_D^{20}$ +19.8 (*c* 0.40, H_2O); rep. as a yellow oil, $[\alpha]_D^{20}$ +10.9 (*c* 0.11, H_2O)[12d]]. To obtain hyacinthacine A_2 (**3**), the alcohol **18** was converted into the corresponding mesylate **21**, which was reduced with $LiAlH_4$ to give the protected trihydroxypyrrolizidine **22**. Final hydrogenation over Pd afforded hyacinthacine A_2 (**3**) as a colourless oil, which



Scheme 3. *Reagents and conditions*: (a) Zn, CH_3COOH/H_2O, 50°C, 4 h, 80%; (b) $LiAlH_4$, THF, reflux, 1.5 h, 75% for 19, 40% for 22; (c) H_2, Pd/C, MeOH, rt, 3 d, 76% for 20, 75% for 3; (d) MsCl, TEA, CH_2Cl_2, rt, 2 h, 100%.

showed spectroscopic and analytical properties in agreement with those reported for the natural product[5,11a] [$[\alpha]_D^{24}$ +12.7 (*c* 0.13, H_2O); rep. $[\alpha]_D$ +12.5 (*c* 0.4, H_2O),[11a] $[\alpha]_D$ +20.1 (*c* 0.44, H_2O)[5]].

In conclusion, the reported syntheses of nitrone **8** allow a straightforward and completely stereoselective entry to polyhydroxypyrrolizidines, as demonstrated by the total syntheses of 7-deoxycasuarine (**20**) and hyacinthacine A_2 (**3**) in only seven steps and 24% overall yield and eight steps and 13% overall yield, respectively, from tribenzyl derivative **5** or **9**, that compare very well with the only previously reported syntheses of **20**[12d] and **3**[11a] which are affected by very poor selectivities.

Studies are currently underway in our laboratory to extend this method to the synthesis of a broad range of alexines, casuarines, hyacinthacines and pyrrolidine alkaloids and analogs.

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14. All new compounds were fully characterized and gave satisfactory spectroscopic and analytical data.
15. (3*R*,4*R*,5*R*)-3,4-Dibenzyloxy-5-benzyloxymethyl-1-pyrroline *N*-oxide (**8**): white solid, mp 80–82°C; $[\alpha]_D^{19}$ −41.7 (*c* 1.00, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.38–7.26 (m, 15 H), 6.91 (d, $J=1.9$ Hz, 1 H), 4.69–4.67 (m, 1 H), 4.64–4.46 (m, 6 H), 4.39 (dd, $J=3.2$, 2.2 Hz, 1 H), 4.10–4.04 (m, 2 H), 3.78 (d, $J=7.3$ Hz, 1 H); ^{13}C NMR: δ 137.7 (s), 137.2 (s), 137.1 (s), 132.9 (d), 128.6, 128.5, 128.4, 128.1, 127.9 and 127.7 (d, 15 C), 82.7 (d), 80.3 (d), 77.4 (d), 73.9 (t), 71.9 (t), 71.6 (t), 66.1 (t). Anal. calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.51; H, 6.78; N, 3.01%.
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